Through ketamine fields

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DOI:
10.33612/diss.107955714

CHAPTER 3

SPECIAL FEATURES OF SPECIAL K: APPLICATIONS FOR PAIN AND DEPRESSION TREATMENTS

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Published in the book "Breaking Convention: psychedelic pharmacology for the 21st century"
London, 2017, Strange Attractor Press
Lead editor: Ben Sessa
ISBN: 978-1-907222-55-9

Part 1

It hurts

The International Association for the Study of Pain defines pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage (1). The mechanisms by which tissue injuries produce a state of pain represent one of the most intensely investigated areas in the biomedical sciences over several years (2).

Glutamate, the major excitatory neurotransmitter in the brain and spinal cord, exerts its postsynaptic effects via a diverse set of membrane receptors. Notably, the N-methyl-D-aspartate (NMDA) receptors have received particular attention because of their crucial roles in excitatory synaptic transmission, plasticity and neurodegeneration in the central nervous system (2).

Ketamine, also known as "special K", increases the presynaptic release of glutamate, resulting in higher extracellular levels of glutamate by a combination of disinhibition of the neurotransmitter γ-aminobutyric acid (GABA) and blockage of the NMDA receptors at the phencyclidine site within the ion channel (3). This increase in extracellular glutamate release favours co-expressed α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), resulting in an increased glutamatergic throughput of AMPA relative to NMDA (3).

Ketamine is a well-known human anaesthetic, with analgesic effects that may be used to treat pain in a range of disorders (4). In the field of pain management, there is ample experience with oral as well as intravenous (IV) applications of ketamine. Indications for ketamine include neuropathic pain of various origins, complex regional pain syndrome, cancer pain, orofacial pain, and phantom limb pain.

There is considerable evidence that pain associated with peripheral tissue or nerve injury involves NMDA receptors activation (5). Consistent with this, NMDA receptor antagonists have been shown to effectively alleviate pain-related behaviour (6-21). However, the use of NMDA receptor antagonists can often be limited by serious side effects, such as memory impairment, psychotomimetic effects, ataxia, and motor incoordination (2).

Part 2

Some relief

Ketamine is a non-selective NMDA receptors antagonist and due to the presence of a chiral centre, it has two enantiomers (figures 3.1 and 3.2): S-ketamine and

R-ketamine. The S-enantiomer is marketed in Europe (trade name "ketanest"); the rest of the world makes use of the racemic mixture (trade name "ketalar") (22).

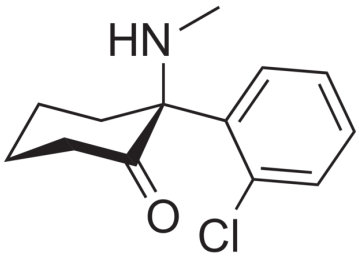

Figure 3.1: S-ketamine (23)

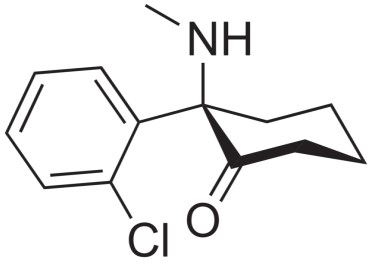

Figure 3.2: R-ketamine (24)

Ketamine is effective in acute and chronic pain with important differences in pharmacodynamics between these pain states. Analgesia induced by ketamine for acute pain relief is driven by the drug's pharmacokinetics with a short half-life of effect (one to ten minutes) and displays an immediate loss of analgesia upon the termination of ketamine administration. On the other hand, analgesia for neuropathic pain relief is best induced via a long-term infusion, with treatments lasting days (even weeks) rather than hours, making the analgesia persistent for days and weeks beyond the exposure time (half-life for effect: ten to eleven days) (22).

Ketamine metabolism happens in the liver through the cytochrome P450 enzyme system. Ketamine metabolites include norketamine (80%), hydroxynorketamine (15%) and hydroxyketamine (5%). In humans, these metabolites have a limited contribution to ketamine effect. The N-demethylation into norketamine is the major metabolic pathway. At clinical concentrations, N-demethylation is catalised

by CYP3A4 and CYP2B6. All metabolites undergo glucuronidation, followed by elimination via kidneys and liver, with 10 to 20% of ketamine being excreted unchanged (25,26).

The most common side effects of IV ketamine are psychotomimetic effects and dissociative symptoms (27), such as confusion, dizziness, euphoria, elevated blood pressure and increased libido, although all of these usually dissipate within two hours of IV infusion (28,29). The increased blood pressure can be managed with the concomitant use of a benzodiazepine (8,11).

Another concern with ketamine is its abuse potential. Ketamine has been used recreationally since the 1960's. The so-called "side effects" (hallucinations and dissociative experiences) might be perceived as "desired effects" by people with psychonautic purposes. Psychonautics refers both to a methodology for describing and explaining the subjective effects of drugs, and to a long-established research paradigm in which intellectuals have taken drugs to explore human experience and existence (30). Some of the most well-known examples of psychonautics research include work by Aldous Huxley (notably with mescaline), John C. Lilly (mainly with ketamine), and Alexander and Ann Shulgin (especially with ecstasy-type drugs) (30,31).

An important reason to focus on NMDA receptor antagonists is that current treatment paradigms based on antidepressants, antiepileptics, slow-release opioid, and local treatment (e.g. lidocaine or capsaicine patches) are only effective in 30% of patients. Therefore, there is the urgent need for an additional treatment that will cover a larger percentage of patients (22).

The most effective ketamine treatment is by IV infusion. This in-house therapy is expensive and there is the need for at home ketamine treatment possibilities. Currently this is possible, for example, by using oral or intranasal ketamine. However, due to a low bioavailability, the probability of long-term success is restricted. Concerning bioavailability, it should be noted that this is only between 17% (32) and 23% (33) in oral administration, because its extensive first-pass metabolism (32). Intranasally, ketamine has a bioavailability of 45% (34). Furthermore, the currently marketed ketamine solution is bitter, lowering patient compliance and adherence to therapy. Niesters and Dahan (2012) recommend that new modes of administration need to be developed. The expectation is that new modes of administration should be well accepted and should have a higher bioavailability (22).

Therefore, extensive knowledge on the pharmacokinetics and pharmacodynamics of ketamine, its enantiomers and its metabolites is required, so that careful treatment of the patient can be possible, aimed at optimal pain relief combined with minimal side effects.

Part 3

But life still sucks

Depression is a very common mental disorder. Globally, more than 350 million people of all ages suffer from depression. It is the leading cause of disability and economic burden worldwide (35). Although there are medications that alleviate depressive symptoms, these have serious limitations. Most notably, available treatments require weeks or months to produce a therapeutic response, and only about one-third of patients respond to the first medication prescribed (36,37).

Hallucinogenic drugs produce alterations in consciousness, perception, thought, and emotion. They have been used recreationally and entheogenically for millennia. Entheogens constitute a class of psychoactive substances that induce any type of spiritual experience aimed at development or sacred use; the term "entheogen" is often chosen to contrast recreational use of the same drugs. The so-called "classical" psychedelic drugs such as lysergic acid diethylamide (LSD), psilocybin, dimethyltryptamine (DMT), and mescaline are thought to exert their effects through agonism at the 5-HT_{2A} receptors. Dissociative hallucinogens including ketamine, phencyclidine (PCP) and dextromethorphan (DXM) act primarily as NMDA glutamate receptor antagonists (38,39). The subjective state of dissociation from the body commonly experienced after sufficiently high doses of ketamine is called "K-hole" (40).

There has been growing interest in the observation that ketamine has a rapid positive effect on depressive symptoms. It has been more than a decade since ketamine, an anaesthetic medication, was first reported to have therapeutic effects in depression (39). The fact that ketamine does not work through the conventional antidepressant monoaminergic targets of serotonin and noradrenaline has provoked excitement and understanding its effects could provide novel insights into the pathophysiology of depression and open up a new class of medications (39). A study performed with rats has shown that the mechanisms underlying this effect involve the activation of the mammalian target of rapamycin (mTOR) pathway and increases spine formation and synaptic transmission in the prefrontal cortex (36).

Current pharmacologic treatments for depression consist of a usual armamentarium of more than 24 antidepressants with at least seven different mechanisms of action (37). Some studies state that the effects of ketamine occurred only at low doses, indicating that the antidepressant actions of ketamine need not be accompanied by psychedelic side effects (38,41). Ketamine is inexpensive and easy to administer. It also has a rapid onset of action and minimal side effects when used at subanaesthetic doses (42).

Several studies demonstrate that ketamine is capable of inducing a robust antidepressant effect in patients with depression, which were previously refractory to standard treatment with oral antidepressants as well as electroconvulsive therapy (38,41,43-49).

Part 4

A pill for all pains?

With a team of researchers from the University of Groningen, I performed a literature review about the use of ketamine to treat depression and pain. It has been published in the British Journal of Psychiatry (29) and its whole version is presented in the second chapter of this thesis, with supplementary material available in appendices 1 and 2.

As mentioned in chapter 2, we concluded that, in the field of pain management, there is ample experience with the oral as well as IV applications of ketamine. As in depression, the analgesic effect is believed to be based on antagonism of NMDA receptors. The majority of the analysed pain studies used the IV application of ketamine; the doses used differed from 0.1 to 62 mg/kg/day. It was not possible to establish a dose-response association, but the majority of the analysed pain studies described ketamine as effective in reducing pain, even with low oral doses (29).

One study deserved a remark: the green bubble number 53 representing a study by Villanueva-Perez et al. (2007) – see figure 2.2 in chapter 2. In this study, oral ketamine was administered daily for 660 days at a dose of 3.4 mg/kg/day in one patient, with a significant improvement and non-severe side effects (50).

Similarly, the majority of the analysed depression studies also used the IV application of ketamine. The most common doses were 0.5 mg/kg/day and other smaller doses, as we can see in the huge overlap of points close to the intersection of the x and y-axis – see figure 2.1 in chapter 2. The highest dose applied in a depression study was 36 mg/kg/day in two patients (51). They had a very significant response with non-severe side effects (mild feeling of headiness).

The doses used for depression were in the lower range compared to studies that investigated analgesic use. Also, ketamine as an antidepressant was generally given for shorter durations than ketamine as an analgesic.

We found no evidence for neurotoxicity caused by ketamine at therapeutic doses. Nevertheless, it is known that prolonged ketamine abuse has been associated with memory changes (52), cognitive impairment (27,53), white matter changes (54), and reduced well-being (27). Also, inflammation and damage to the ureters and bladder

are well documented in heavy ketamine users, i.e. consumption of approximately 80 mg/kg/day, which is more than two times higher than the highest dose found in a study where ketamine was used to treat depression. Side-effects commonly mentioned were dizziness, hallucinations, nausea, vomiting, drowsiness, confusion, light-headedness, headache, somnolence, and anxiety. Adverse events did not persist after ketamine discontinuation. Interestingly, these side effects were not reported as a burden in treatment maintenance (29).

Part 5

The afterglow

From our literature review, we concluded that there is enough scientific ground for future trials to incorporate longer treatment durations for depression based on the experience with ketamine in pain trials.

The reason why ketamine is still not officially approved as an analgesic and as an antidepressant might be controversial. There is vast scientific background showing that ketamine has manageable side effects, just as several drugs approved and being marketed at this moment. The fact that ketamine is an old drug (therefore, off-patent) that would not make a big profit for the pharmaceutical industry if marketed as an analgesic or antidepressant should not be ignored.

The rapid antidepressant effect of a single sub-anaesthetic IV dose of ketamine is one of the most significant conceptual breakthroughs in the pharmacological treatment of depression in decades. Ketamine has been proving to be a useful tool in treating depression and pain, and the fact that it is not being widely applied in current medicine is probably due to the stigma associated with its recreational use more than with the harm that it can cause in a medical setting. Although not official, the antidepressant and the analgesic uses of ketamine are already legitimate.

Statement of conflicts of interest

The author declares no conflict of interest.

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